REMARKS

Reconsideration and continuing examination of the above-identified application is respectfully requested in view of the amendments above and the discussion that follows.

Each of the independent claims has been amended, as have several of the dependent claims as is discussed below. Claims 1-9, 12-17, 19-33, 35-38 and 42-78 are in the case and are before the Examiner.

I. The Amendments

Each of independent claims 1, 18, 42, 51, 63, 75 and 78 has been amended to cancel the limitation that a substitution is conservative to speed prosecution. Support for the fact that the substitutions are or can be conservative is noted at least in paragraphs [0152-0157] of the published application (20030138769) that discuss various aspects of substitutions and begin in paragraph [0152] by asserting that "a contemplated chimer molecule can also contain conservative substitutions in the amino acid residues that constitute HBc Domains I, II, III and IV". In addition, original claims 1, 63 and 79 used "conservatively substituted" along with 20, 10 and 20 percent substitutions, respectively. Nonetheless, the clarifying amendment has been cancelled to speed prosecution.

Claims 1 and 63 have been amended to improve their syntax. Claim 51 has also been amended by addition of features recited in claim 1.

Claims 1, 18, 42, 51, and 63 have been amended to clarify the stability that is exhibited by the constructs. This stability is directed at the proteins themselves as is seen from the SDS-PAGE gel results shown in Figs. 3, 4 and 8 and the disclosures at least at Paragraphs [0093], [0353-0362] and

Examples 6, 7, as well as Examples 22 and 23 Paragraphs [0481-0493].

Claims 52-62 and 64-78 have been amended to change "particle" to "particles", to thereby provide agreement with the independent claims.

It is thus seen that no new matter has been added.

II. The Action

A. Rejections Under 35 USC §112,

First Paragraph

It is noted with appreciation that the prior rejection based on the First Paragraph of Section 112 has been withdrawn. It is believed that the newly asserted rejection under the First Paragraph of Section 112 for the presence of alleged new matter is moot in view of the present amendments.

B. Rejection Under 35 USC §103(a):

Pumpens In View Of Zlotnick

Withdrawal of the rejection of claims 12-14, 17, 27-29, 36, 37, 59-62 and 76 as allegedly obvious over the disclosures of Pumpens (1995), in view of Zlotnick is noted with appreciation. The rejection of claims 1-9, 15, 16, 18-26, 30-33, 355, 38, 42-58, 63-75, 77 and 78 over the combined teachings of that same art that was asserted in the previous Action has been maintained here. This rejection is again respectfully traversed as discussed hereinbelow.

The present Action has reiterated the rejection from the previous Action. Following the logic of that Action, only the invention of new elements as was done when Elements 95 and 96 were claimed by the late Glenn T. Seaborg in US Patents No. 3,156,523 and No. 3,161,462, respectively, would be sufficiently free of pre-existing elements to gain patentability.

Here, (i) HBc proteins that contained added non-HBc sequences but were unstable on storage existed in the art. It was also known from Zlotnick that (ii) elimination of all internal cysteine residues from a truncated HBc protein plus the addition of a single heterologous residue at the C-terminus produced particles that could better withstand being in a 3.5 M urea denaturing solution than could particles produced from a similar disulfide-reduced protein or a cysteine-free protein. The reported result from that dunking of particles in denaturant for an unspecified time was that the particles containing the C-terminal cysteine stayed together, whereas those without any cysteines denatured, dissociated and formed two peaks in the size exclusion study shown in Fig. 2b. The results shown in Fig. 2a indicate that the protein of the cysteine-containing chimers polymerized at pH 9.5 were less pure than that polymerized at pH 7.5.

It is respectfully submitted that Zlotnick is, at worst, silent on the issue of protein stability of chimers with and without cysteines. Indeed, it is rather urged from the extra band seen in the monomer region of lane 7 of Zlotnick's Fig. 2a that having the added cysteine caused a protein stability problem with those chimers. Thus, there were two or possibly three protein bands in lane 7 for the cysteine-containing chimer, with only one band being seen for any of the cysteine-free proteins.

It is thus submitted that Zlotnick has no teaching related particle stability in the form of protein degradation, as compared to particle dissociation stability. The claims have been amended to clarify that the stability recited relates to the proteins of the particles. That is what the underlying stability data show. Copies of Figs. 3, 4, and 8 are attached to this paper for the Examiner's convenience.

what may be in the mind of a hypothetical person of ordinary skill. Rather, Ulrich is (was) an author of probably greater than ordinary skill. Ulrich wrote in a peer-reviewed paper published after both relied-on documents and before the filing of the instant application's earliest parent application that a problem of chimer usage in vaccines related to the requirement of reproducible preparation of intact chimer particles that were stable and could withstand long-term storage.

Ulrich did not put together the combination of the two teachings to solve the stability problem that he wrote about, but rather maintained that the problem still had to be solved. Ulrich, Pumpens and other authors published enclosed Exhibit I [Lachmann et al., *Intervirology* 1999; **42**:51-56] about a year prior to the filing of the earliest parental application here and cited the relied-on Zlotnick paper as note [16]. Counsel has found a single reference to [16] and that is on page 55. The point for which Zlotnick was cited is the following:

> Similarly, C-terminal fusions [of inserted peptide sequences] were found again to be lower immunogenic [sic] than c/e1 insertions [8]. These data are in line with structural data suggesting a luminal localization of the C-terminal region [16].

It is submitted that if Ulrich the real, live worker of more than ordinary skill working and writing in this art did not put together the relied-on art as has the hypothetical skilled worker of the Action, the Action is mistaken in its conclusion as to the abilities of its hypothetical worker and obviousness, and that conclusion of obviousness should be withdrawn.

In another published paper entitled "Stability and Morphology Comparisons of Self-Assembled Virus-Like Particles

from Wild-Type and Mutant Human Hepatitis B Virus Capsid Proteins" Newman et al., *J. Virol.*, Dec. 2003; **77(24):**12950-12960, (enclosed Exhibit II), the authors cited the Zlotnick paper at page 12959 as note (39) for

> [u]sing spectrophotometric measurement, Zlotnick et al. estimated the stoichiometry of encapsidated RNA and *E. coli*-derived capsid particles to be near a total of 3,000 ribonucleotides per full-length capsid particle (95% T=4) (39).

The Abstract of that paper states in part:

> [w]e found no significant differences in capsid stability between wild-type and mutant I97L particles [those whose isoleucine at position 97 was mutated to a leucine] under denaturing pH and temperature in either full-length or truncated core protein contexts. In general, HBV capsid particles (HBcAg1-183, HBcAg1-149, and HBcAg1-140) are very robust but will dissociate at pH 2 or 14, at temperatures higher than 75^{o}C, or in 0.1% sodium docecyl sulfate (SDS).

The lead (corresponding) author of Newman et al. is Dr. Chiao Shih, a full Professor in the Departments of Pathology and of Microbiology and Immunology at the University of Texas Medical Branch. Examination of his profile, which was obtained from the University web site and is attached as Exhibit III, shows that he has been the lead author of several peer-reviewed articles dealing with hepatitis B core. It must be agreed that the Newman et al. paper is concerned with particle stability from its title and the second quote above. Thus, from the above quotes, we have another worker of more than ordinary skill in

the art who cited the Zlotnick paper, but failed to make the connection that is asserted to be obvious to a worker of lesser skill; i.e., ordinary skill. It is again submitted that this basis for rejection should be withdrawn.

C. Second Rejection Under 35 USC §103(a)

Pumpens In View Of Zlotnick and Thornton

Claims 12-14, 17, 27-29, 36, 37, 59-62 and 76 were rejected as allegedly obvious from the combined disclosures of Pumpens in view of Zlotnick as above, and further in view of Thornton et al. US Patent No. 5,143,726. The Thornton et al. patent is relied-on for its disclosures of linking a polypeptide to core via "an amino acid side chain on the core molecule . . ." (Action , page 7). This rejection is respectfully traversed as discussed below.

The deficiencies of the combined teachings of Pumpens and Zlotnick from above and the previous discussions are hereby repeated. In addition, the presently rejected claims recite directly or indirectly that the chimeric molecule "contains a heterologous linker residue for a conjugated epitope". Thornton teaches only amino acid side chains that are endogenously present. As such, the skilled worker who did not have the present application in front of him or her would have to alter the sequence of the immunogenic loop with no guidance for doing so.

That Pumpens teaches an amino acid sequence of hundreds of residues can successfully be inserted into the loop does not teach or suggest that one can add a single residue and successfully couple an oligopeptide or oligosaccharide, for example, to an added residue in the same region of a HBc chimer. Zlotnick has no suggestion of even adding a sequence into the

HBc backbone, let alone adding a sequence that is substantially perpendicular to the backbone, nor does Zlotnick suggest what might happen to such a chimer protein on standing in an aqueous buffer for about two weeks. It is submitted that this rejection should be withdrawn.

D. The Zlotnick Teachings are Not Properly Combinable with those of Pumpens

The present Action, like those before it, has improperly combined the teachings of Zlotnick with those of Pumpens. This Action and its predecessors have disregarded the disclosure at Pumpens page 67, left side (underlined) that states:

> [a]lthough capsids formed by C-terminally truncated HBc monomers are less stable than the corresponding full-length protein particles [citations omitted], foreign insertions are not only possible but also exert a stabilizing effect on HBcΔ derivatives, especially in the case of internal insertions [citation to Borisova's unpublished work omitted].

The question must again be asked, "Why would a skilled worker combine the teachings of Pumpens and Zlotnick when Pumpens teaches that one can gain stability in C-terminally truncated chimers by having internal insertions? The answer is that such a worker would not do so.

The skilled worker at the time the invention here was made, trying to obtain the stabilized HBc chimer particle Ulrich said would be useful, would not have combined the teachings of Pumpens with those of Zlotnick. First, that worker would have heeded Pumpens who taught that adding internal sequences to C-terminal polypeptides provided enhanced stability.

Next, once it was found out that Pumpens was incorrect in the statement, that worker still would not have gone to the Zlotnick paper because its title, Abstract, Conclusions and content all provide no implication that it might be useful. Further reading of Zlotnick would also provide no inkling that its teachings should be combined with those of Pumpens, because Zlotnick teaches nothing about the effects that might be obtained when insertions were added to the truncated protein, to say nothing about not mutating the Cys residues at positions 48, 61 and 107 into non-conservative substitutions.

Still further, because Zlotnick teaches about dissociability of the particles and not the stability of the proteins that constitute the particles, that worker gets nothing from Zlotnick that relates to these claims. Rather, the skilled worker would read the later-published Ulrich article and learn that the stability issue of proteins in stored particles for use in vaccines or other inocula had not yet been solved. That skilled worker would therefore understand why the presently claimed invention is not obvious and why the Zlotnick teachings are improperly combined with those of Pumpens or any other art of record.

E. Additional Information That May Be Material

In view of the holding in *McKesson Information Solutions, Inv. V. Bridge Medical, Inc.* (Fed. Cir. May 18, 2007; 06-1517), enclosed herewith are copies of Actions from an application relating to recombinant hepatitis B core particles and their use that might be deemed material to the prosecution of the present application. It is noted that the Examiner handling this application is also handling divisional applications Serial No. 10/805,913 and Serial No. 10/806,006, as well as applications Serial No. 10/732,862 and Serial No.

10/787,734, so the Actions from those applications are not being included herewith. The enclosed Actions are from Application Serial No. 10/677,074, and are noted on enclosed Form PTO/SB/08B.

F. Summary

Independent claims 1, 18, 42, 51, 63, 75 and 78 have been amended have been amended, as have dependent claims 52-62, 64-74 and 76-78. Each of the bases for rejection has been dealt with and overcome or otherwise made moot.

It is therefore believed that this application is in condition for allowance of all of the pending claims. An early notice to that effect is earnestly solicited.

A fee for the filing of the other Actions is enclosed. No further fee or petition is believed to be necessary. However, should any further fee be needed, please charge our Deposit Account No. 23-0920, and deem this paper to be the required petition.

The Examiner is requested to phone the undersigned should any questions arise that can be dealt with over the phone to expedite this prosecution.

Respectfully submitted,

By _____
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Enclosures
- Exhibits I-III.
- Petition and Fee
- IDS Fee for filing Actions
- Actions from other application, Form PTO/SB/08B
- Figs. 3, 4, and 8